REMARKS

The Office Action dated June 14, 2004, has been received and reviewed. Claims 1, 4-11 and 33-34 are pending and stand rejected. Applicants respectfully request reconsideration of the application as amended herein and in view of the arguments below.

I. Claim Amendments

Applicants have amended Claim 1 to recite 95% homology rather than the hybridization language. Support for this amendment may be found on page 12, lines 29-32. Applicants have canceled Claims 8-10, 12-32 and 34 without prejudice or disclaimer.

II. Rejections under 35 U.S.C. § 101

Claims 1, 4-7 and 11 stand rejected under 35 U.S.C. § 101 as allegedly not being supported by a specific and substantial asserted utility or well established utility. Applicants respectfully disagree with this assertion.

This case clearly states an adequate utility consistent with the guidelines set forth in the *Utility Examination Guidelines,* Federal Register 66, 1092 (January 5, 2001). This is not a case where no utility is stated; this is not a case where a vague utility (e.g., "biological activity") is stated; this is not a case where an arguable incredible utility (e.g., treating an intractable disease) is stated; this is not a case where a "throw away" utility is stated. To the contrary, in the present application it is noted that sigma receptors are useful as markers in the non-invasive detection and visualization of a wide variety of tumors using single photon emission computed tomography and positron emission tomography technology. *See,* page 2, lines 4-6. **Additionally, sigma receptors are abnormally expressed, e.g. overexpressed in tumor cells** providing an established use. *See,* page 2, line 31 and page 6, lines 30-32. Particularly, σ_2 receptors were found to be expressed eight to ten times more in proliferative (P) tumor cells than in quiescent (Q) tumor cells. Page 3, lines 33-34. In one study, the σ_2 receptor P:Q ratio was about 10.6 in solid tumors and about 9.5 in a tissue culture study. Wheeler et al., *Br. J. Cancer* 86, 1223-1234 (2000). This would allow one of skill in the art to better diagnose cancer and other disorders of cell proliferation. Applicants note that the specification also states with regard to the sigma 1B receptor, "[b]ecause this new variant exhibits σ_2-like binding, it is useful in the screening of compounds useful in the detection of the proliferation state of tumors, as well as in other uses. The new $\sigma_{1\beta}$ variant finds particular

use in the non-invasive diagnosis of cancer and more particularly in the diagnosis of proliferative cancer cells." Page 5, lines 10-14. Page 6, lines 8-13 notes that the compounds of the present application allow for such uses as diagnostic compounds for the imagining of tumor cells. These compounds are also useful as therapeutics for the treatment of cancer and other disorders of cell proliferation. The ligand compounds of the present application are also useful in methods of determining the proliferative status of a tumor. *See,* page 6, lines 8-13. Furthermore, the methods and compositions of the present invention are useful in relation to non-cancer disorders of cell proliferation. These diseases include, but are not limited to, benign tumors, hyperplasias, hyperpigmentation of the skin, psoriasis, and any other disorder wherein cell proliferation is uncontrolled, and control, diagnosis, or imaging of such proliferation is desired. *See,* page 10, lines 17-22.

Applicants also note that the $\sigma_{1\beta}$ receptor exhibits σ_2-like binding, as described in experimental detail below. It is the σ_2 receptor activity that plays a role for the present application. The σ_2 receptor plays a role in tumor cell proliferation and induction. As such, methods for determining the proliferative state of a cell by determining the cell's ability to bind σ_2 receptors may now be carried out using a cell's ability to bind $\sigma_{1\beta}$. *See*, pages 34-35, lines 32-33 and 1-2. Again, this would allow one of skill in the art to better diagnose cancer and other disorders of cell proliferation. Applicants further note that these methods for determining the proliferative status of cancer cells are carried out by determining the ability of proliferative cells to bind σ_1 and $\sigma_{1\beta}$ ligands, respectively. The ratio of $\sigma_{1\beta}$ to σ_1 density on a cell is an indicator of the proliferative state of the cell. Applicants further note that Φ receptors have been defined as nonopiate, nondopaminergic, and nonphencyclidine receptors based on their ligand binding characteristics. *See, e.g.*, Thomas, *Life Sci.* 46:1279-1286 (1990); Bem, et al., *Cancer Res.* 51: 6558-6562 (1991); John, et al., *J. Nucl. Med.* 37:267P (1996); John, et al., *J. Nuc. Med.* 34:2169-2175 (1993); John, et al., *J. Med. Chem.* 37:1737-1739 (1994); John, et al., *Life Sci.* 56:2385-2392 (1995); John, et al., *J. Nucl. Med.* 37:205P (1996). Thus, the present application allows for one of skill in the art to determine the proliferative status of σ_{1B} and determine a ratio of σ_{1B} activity in tumor regions of interest versus normal tissue. Accordingly, there is a well established utility for σ_{1B}. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1, 4-7, 11 and 33.

III. Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1, 4-7, 11 and 33 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse these rejections due to the amendments to the claims and the reasons enumerated in the response to the 35 U.S.C. § 101 rejections and enumerated below.

Applicants note that the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (MPEP §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Applicants note that Claims 1 and 11 to recite specific structurally related sequences which encode for a $\sigma_{1\exists}$ receptor whose functionality and biological activity has been disclosed throughout the specification. It is the fact that the $\sigma_{1\exists}$ receptor exhibits σ_2-like binding that enables the present application. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1, 4-7, 11 and 33.

IV. Rejections under 35 U.S.C. § 112, first paragraph (written description)

Claims 1, 4-7, 11 and 33 also stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not containing subject matter described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. Applicants respectfully disagree with this assertion for the reasons enumerated in the previous sections and for the reasons discussed below.

Applicants note that the United States Patent and Trademark Office has provided guidelines regarding the policy objectives of the written description requirement. The guidelines explain that the policy goals are to i) clearly convey to the public what was invented; ii) put in possession of what the applicant claims as the invention; and iii) prevent an applicant from claiming subject matter that was not described in the specification as filed.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1104-05 (Jan. 5, 2001). Applicants note that the specification discloses that SEQ ID NO:1 is the human mRNA (cDNA) sequence of $\sigma_{1\beta}$, and SEQ ID NO:2 is the human $\sigma_{1\beta}$ amino acid sequence. Therefore, the structure of the invention has been clearly established and one of skill in the art could readily predict the structure as claimed. Applicants have additionally amended Claim 1 to recite that the polynucleotides comprising SEQ ID NO: 1 or that encode SEQ ID NO: 2 are at least 95% similar to SEQ ID NO: 1 or SEQ ID NO: 2 and encode a $\sigma_{1\beta}$ receptor. Applicants have provided hybridization condition for such activity. Applicants further note that it may be advantageous to produce nucleotide sequences encoding $\sigma_{1\beta}$ or its derivatives possessing a substantially different codon usage. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding $\sigma_{1\beta}$ and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence. Applicants further submit that for the reasons discussed above, there is clear evidence of activity of a $\sigma_{1\beta}$ receptor. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph rejections.

Additionally, Applicants note that the United States Patent and Trademark Office has clarified the standard for examining applications for compliance with respect to the written description requirement of 35 U.S.C. §112, first paragraph. These guidelines state, in part:

> The examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed . . . . Consequently, rejection of an original claim for lack of written description should be rare.

66 Fed. Reg. 1099, 1105 (Jan. 5, 2001) (emphasis added). Applicants respectfully contend that the specification does provide a sufficient written description so that one skilled in the art would appreciate that the Applicant was in possession of the claimed invention at the time of filing. Applicants submit that a person of skill in the art can readily envision polynucleotides

comprising SEQ ID NO. 1, encoding SEQ ID NO.2 or active fragments thereof. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph to Claims 1, 4-7, 11 and 33.

V. 35 U.S.C. § 102, anticipation rejections

Claim 33 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Malliga et al. Applicants respectfully traverse this rejection as set forth below.

Case law holds and the M.P.E.P. states that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, the identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Additionally, anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention. *Apple Computer Inc. v. Articulate Systems Inc.* 57 USPQ2d 1057, 1061 (Fed. Cir. 2000).

Applicants submit that Malliga et al. does not anticipate the present invention. Applicants submit that Malliga fails to disclose the peptides of Claim 1. Therefore, the transformed cell comprising the polynucleotide of Claim 1 would not be disclosed by Malliga et al. Applicants submit that Claim 33 is novel as each and every element of the invention is not disclosed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection to Claim 33.

ENTRY OF AMENDMENTS

The amendments to the claims above should be entered by the Examiner because the amendments are supported by the as-filed specification and drawings and do not add any new matter to the application. Further, Applicants believe that the amendments do not raise new issues or require a further search. Applicants further submit that the amendments should be allowed pursuant to 37 C.F. R. § 1.116, because amendments after final representing rejected claims in better condition for allowance may be admitted.

CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney, Jarett K. Abramson, at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully Submitted,

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